III. Detection and Evaluation

ATP III recognizes that detection of cholesterol disorders and other coronary heart disease (CHD) risk factors occurs primarily through clinical case finding. Risk factors can be detected and evaluated as part of a person's work-up for any medical problem. Alternatively, public screening programs can identify risk factors, provided that affected individuals are appropriately referred for physician attention. The identification of cholesterol disorders in the setting of a medical examination has the advantage that other cardiovascular risk factors—including prior CHD, PVD, stroke, age, gender, family history, cigarette smoking, high blood pressure, diabetes mellitus, obesity, physical inactivity—co-morbidities, and other factors can be assessed and considered prior to treatment.

At the time of physician evaluation, the person's overall risk status is assessed. Thus, detection and evaluation of cholesterol and lipoprotein problems should proceed in parallel with risk assessment for CHD. The approach to both is described below.

1. Identification of risk categories for setting of LDL-cholesterol goals

The guiding principle of ATP III is that the intensity of LDL-lowering therapy should be adjusted to the individual's absolute risk for CHD. In applying this principle, ATP III maintains that both short-term (≤10-year) and long-term (>10-year) risk must be taken into consideration. Thus, treatment guidelines are designed to incorporate risk reduction for both short-term and long-term risk (composite risk). ATP III identifies three categories of risk for CHD that modify goals and modalities of LDL-lowering therapy: established CHD and CHD risk equivalents, multiple (2+) risk factors, and 0–1 risk factor (Table III.1–1).

Table III.1–1. Categories of Risk for Coronary Heart Disease (CHD)

Risk Categories
Established CHD & CHD risk equivalents
Multiple (2+) risk factors
0–1 risk factor

a. Identification of persons with CHD and CHD risk equivalent

Coronary heart disease. Persons with CHD are at very high risk for future CHD events (10-year risk >20 percent). Several clinical patterns constitute a diagnosis of CHD; these include history of acute myocardial infarction, evidence of silent myocardial infarction or myocardial ischemia, history of unstable angina and stable angina pectoris, and history of coronary procedures (coronary angioplasty and coronary artery surgery).

Other clinical atherosclerotic diseases. Persons in this subcategory have a CHD risk equivalent. Included are those with peripheral arterial disease, abdominal aortic aneurysm, carotid artery disease (symptomatic [e.g., transient ischemic attack or stroke of carotid origin] or

>50 percent stenosis on angiography or ultrasound), and likely other forms of clinical atherosclerotic disease (e.g., renal artery disease).

Diabetes mellitus. ATP III counts diabetes as a CHD risk. The current criteria for the diagnosis of type 2 diabetes from the American Diabetes Association (ADA) are a fasting plasma glucose ≥126 mg/dL and/or 2-hour plasma glucose (after a standard 75 mg glucose load) ≥200 mg/dL (American Diabetes Association 1998). The current ADA recommendations de-emphasize the oral glucose tolerance test in routine clinical care, so it is expected that most people with diabetes will be diagnosed by a fasting glucose level.

Multiple risk factors (10-year risk for CHD >20 percent). Based on 10-year risk assessment using Framingham scoring (see below), a person in this category can be said to have a CHD risk equivalent.

b. Risk assessment in persons without CHD or CHD risk equivalents (starting with risk factor counting)

ATP III's primary approach to risk assessment for persons without CHD or CHD risk equivalents is to count the number of major risk factors for CHD. For persons with multiple (2+) risk factors, a second step is to carry out 10-year risk assessment for CHD. There are two essential reasons for estimating 10-year risk in persons with multiple risk factors: (a) to identify those who have a 10-year risk >20 percent (CHD risk equivalent), and (b) to identify those with borderline high LDL cholesterol who have a 10-year risk of 10–20 percent. Both groups are candidates for more intensive LDL-lowering therapy than was recommended in ATP II.

An alternative approach, which gives similar though not identical results, is to begin with 10-year risk assessment, followed by counting of risk factors in persons with a 10-year risk for CHD <10 percent. This sequence is recommended by advocates of "global risk assessment." The sequence of risk assessment depends on personal choice. It should be noted that beginning with 10-year risk assessment is consistent with approaches recently proposed in other guidelines. Nevertheless, ATP III stratifies risk below 10 percent on the basis of the number of risk factors and not on projected 10-year risk.

The major independent risk factors identified in risk factor counting include:

- Cigarette smoking
- Hypertension (BP ≥140/90 mm Hg or on antihypertensive medication)
- Low HDL cholesterol (<40 mg/dL)
- Family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years)
- Age (men ≥45 years; women ≥55 years)

If a person has a high HDL cholesterol (≥60 mg/dL), one risk factor is subtracted from the count. If the person has type 2 diabetes, this person is classified as having a CHD risk equivalent (see Section II.12.b).

1) Identification of persons with multiple (2+) risk factors

The second risk category that modifies LDL goals includes persons with multiple (2+) risk factors. Approaches to clinical evaluation of risk factors that define the person with multiple (2+) risk factors are shown in Table III.1–2.

Table III.1–2. Clinical Evaluation to Identify Persons with Multiple (2+) Risk Factors

Risk factor	Definition	Comments
Cigarette smoking	Any cigarette smoking in the past month	
Hypertension	Blood pressure ≥140/90 mm Hg or taking antihypertensive medications	Multiple measures of blood pressure required for diagnosis (see JNC VI for further clinical evaluation) (JNC VI 1997; Joint National Committee . . . 1997)
Low HDL cholesterol	HDL cholesterol <40 mg/dL	
Family history of premature CHD	Clinical CHD or sudden death documented in 1st-degree male relative before age 55 or in 1st-degree female relative before age 65	

2) Calculation of 10-year CHD risk

The person with multiple risk factors is assigned to one of three categories according to 10-year risk for hard CHD (myocardial infarction + CHD death): >20 percent, 10–20 percent, and <10 percent (see Table III.1–3). A person with 10-year risk >20 percent is elevated to the category of CHD risk equivalent.

Table III.1–3. Categories of 10-Year Risk for Persons with Multiple (2+) Risk Factors

Risk Categories
>20% (CHD risk equivalents)
10–20%
<10%

Risk assessment for determining 10-year risk is carried out according to Framingham risk scoring (Tables III.1–5 for men and III.1–6 for women). Risk factor scoring in ATP III derives from an update of the Framingham database and methodology reported by Wilson et al., 1998; the revised scoring applies specifically to hard CHD. The risk factors included in the Framingham calculation of 10-year risk are: age, total cholesterol, HDL cholesterol, systolic blood pressure, treatment for hypertension, and cigarette smoking. The first step is to calculate the number of points for each risk factor. For initial assessment, values for total cholesterol and

HDL cholesterol are required. Because of a larger database, Framingham estimates are more robust for total cholesterol than for LDL cholesterol. Note that the LDL-cholesterol level is the primary target of therapy. Total cholesterol and HDL-cholesterol values should be the average of at least two measurements obtained from lipoprotein analysis. The average of several blood pressure measurements, as recommended by JNC VI (JNC VI 1997; Joint National Committee . . . 1997), is needed for an accurate measure of baseline blood pressure. The blood pressure value used in the risk score is the average of several recent values, regardless of whether the person is on antihypertensive therapy. However, if the person is on antihypertensive treatment, an extra point is added beyond points for the blood pressure reading because treated hypertension carries residual risk. The designation "smoker" means any cigarette smoking in the past month. The total risk score sums the points for each risk factor. The 10-year risk for myocardial infarction and coronary death is estimated from total points, and the person is categorized according to absolute 10-year risk as indicated above.

The primary endpoint for 10-year risk assessment in ATP III is "hard CHD" (myocardial infarction and CHD death). However, previous Framingham risk scoring provided estimates of total CHD (stable angina, unstable angina, myocardial infarction, and CHD death). Generally, estimates for hard CHD are about two-thirds to three-fourths of those for total CHD. An exception is for women whose 10-year risk is <10 percent. Estimates of hard CHD for these women can be significantly lower than for total CHD because of the high prevalence of angina pectoris in middle-aged women without evident coronary atherosclerotic disease. Although ATP III does not recommend use of Framingham risk scores for total CHD, it has been adopted in various European countries in accord with guidelines of European cardiovascular societies. Should Framingham scores for total CHD be employed, the approximate equivalency for the three subcategories of risk for persons with multiple (2+) risk factors is listed in Table III.1–4.

Table III.1–4. Approximate Equivalency of Subcategories of Hard and Total CHD According to Framingham Risk Scoring (modified from Wilson et al., 1998)

Hard CHD*	Total CHD†
>20% (CHD Risk Equivalent)	>25% (CHD Risk Equivalent)
10–20%	15–25%
<10%	<15%

* Hard CHD endpoints: myocardial infarction + CHD death.

† Total CHD endpoints: myocardial infarction + CHD death + "coronary insufficiency" (unstable angina) + angina pectoris.

Ten-year risk for hard CHD can be estimated for men and women from Tables III.1–5 and III.1–6, respectively (note that charts for men and women have different scales, so point scores for the two sexes cannot be directly compared). Tables III.1–5 and III.1–6, which approximate the Framingham equations, are provided as a convenient way to estimate 10-year CHD risk using a "paper-and-pencil" approach. Improved methods of assessing 10-year CHD risk will undoubtedly be developed in the future.

It should be noted that the Framingham equations for 10-year CHD risk are not intended to be used to track changes in risk over time as risk factors are modified. The 10-year risk calculation is intended to be performed at the outset to help guide decisions about the intensity of therapy. Thereafter, the clinical trial results are the best guide to the change in risk that accompanies reductions in the risk factors.

In Tables III.1–5 and III.1–6, note that the points for total cholesterol and cigarette smoking decline with age. At face value, this decline is in accord with reports that relative risk for CHD for these two parameters decreases with advancing age. However, this decline is more apparent than real because of the exponential rise in risk with mounting Framingham points. Thus, in older persons who have several points due to age alone, the addition of fewer points for high total cholesterol or smoking increases absolute risk as much or more as do more points at a younger age. Thus, the data in Tables III.1–5 and III.1–6 should not be misconstrued to mean that these risk factors decline in importance with advancing age. The correctness of this conclusion is shown by the same relative benefit in risk reduction obtained with LDL-lowering therapy or smoking cessation in older persons as in younger persons.

Table III.1–5. Estimate of 10-Year Risk for Men (Framingham Point Scores)

Age	Points
20–34	-9
35–39	-4
40–44	0
45–49	3
50–54	6
55–59	8
60–64	10
65–69	11
70–74	12
75–79	13

Total Cholesterol	Points at Ages 20–39	Points at Ages 40–49	Points at Ages 50–59	Points at Ages 60–69	Points at Ages 70–79
<160	0	0	0	0	0
160–199	4	3	2	1	0
200–239	7	5	3	1	0
240–279	9	6	4	2	1
≥280	11	8	5	3	1

	Points at Ages 20–39	Points at Ages 40–49	Points at Ages 50–59	Points at Ages 60–69	Points at Ages 70–79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL	Points
≥60	-1
50–59	0
40–49	1
<40	2

Systolic BP	If Untreated	If Treated
<120	0	0
120–129	0	1
130–139	1	2
140–159	1	2
≥160	2	3

Point Total	10-Year Risk	Point Total	10-Year Risk
<0	<1%	11	8%
0	1%	12	10%
1	1%	13	12%
2	1%	14	16%
3	1%	15	20%
4	1%	16	25%
5	2%	≥17	≥30%
6	2%		
7	3%		
8	4%		
9	5%		
10	6%		

Table III.1–6. 10-Year Risk Estimates for Women (Framingham Point Scores)

Age	Points
20–34	-7
35–39	-3
40–44	0
45–49	3
50–54	6
55–59	8
60–64	10
65–69	12
70–74	14
75–79	16

Total Cholesterol	Points at Ages 20–39	Points at Ages 40–49	Points at Ages 50–59	Points at Ages 60–69	Points at Ages 70–79
<160	0	0	0	0	0
160–199	4	3	2	1	1
200–239	8	6	4	2	1
240–279	11	8	5	3	2
≥280	13	10	7	4	2

	Points at Ages 20–39	Points at Ages 40–49	Points at Ages 50–59	Points at Ages 60–69	Points at Ages 70–79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL	Points
≥60	-1
50–59	0
40–49	1
<40	2

Systolic BP	If Untreated	If Treated
<120	0	0
120–129	1	3
130–139	2	4
140–159	3	5
≥160	4	6

Point Total	10-Year Risk	Point Total	10-Year Risk
<9	<1%	20	11%
9	1%	21	14%
10	1%	22	17%
11	1%	23	22%
12	1%	24	27%
13	2%	≥25	≥30%
14	2%		
15	3%		
16	4%		
17	5%		
18	6%		
19	8%		

2. Determination and classification of LDL cholesterol

a. Who should be tested for cholesterol and lipoproteins?

A fasting lipoprotein profile including major blood lipid fractions, i.e., total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride, should be obtained at least once every 5 years in adults age 20 and over. The rationale for starting cholesterol testing in young adults is described in Sections II.7.j and VIII.4. Since risk categories change slowly over time, the panel judged that lipoprotein measurements once every 5 years are adequate in otherwise low-risk persons. More frequent measurements are required for persons with multiple risk factors or, in those with 0–1 risk factor, if the LDL level is only slightly below the goal level, as will be described subsequently (see Table IV.2–5). If the testing opportunity is nonfasting, only the values for total cholesterol and HDL will be usable. In otherwise low-risk persons (0–1 risk factor), further testing is not required if the HDL-cholesterol level is ≥40 mg/dL and total cholesterol is <200 mg/dL. However, for persons with multiple (2+) risk factors, lipoprotein measurement is recommended as a guide to clinical management.

b. Procedures of measurement

A lipoprotein profile involving measurement of triglycerides and the indirect calculation of LDL cholesterol (the common method) requires a 9- to 12-hour fast. Individuals should be seated for at least five minutes prior to phlebotomy to avoid hemoconcentration. Blood should be collected in tubes without anticoagulant for serum or with EDTA for plasma. Plasma produces values approximately 3 percent lower than serum.

The measurement of any lipid is preferably performed with the person in a baseline stable condition, that is, in the absence of acute illnesses including stroke, trauma, surgery, acute infection, weight loss, pregnancy, or recent change in usual diet. These conditions often result in values that are not representative of the person's usual level.

In persons admitted to the hospital for acute coronary syndromes or coronary procedures, lipid measurements should be taken on admission or within 24 hours. These values can guide the physician on initiation of LDL-lowering therapy at discharge. LDL cholesterol levels begin to decline in the first few hours after a coronary event and are significantly decreased by 24–48 hours and may remain low for many weeks. Thus, the initial LDL cholesterol level obtained in the hospital may be substantially lower than is usual for the patient. Nevertheless, values obtained during the acute phase provide guidance for initiating LDL-lowering therapy.

LDL cholesterol is routinely estimated from measurements of total cholesterol, total triglycerides, and HDL cholesterol in the fasting state. If the triglyceride level is below 400 mg/dL, this value can be divided by five to estimate the VLDL-cholesterol level. Since total cholesterol is the sum of LDL cholesterol, HDL cholesterol, and VLDL cholesterol, LDL cholesterol can be calculated as follows (Friedewald et al., 1972):

$$\text{LDL cholesterol} = \text{total cholesterol} - \text{HDL cholesterol} - \text{triglycerides}/5$$
(where all measures are in mg/dL)

For persons with triglycerides over 400 mg/dL, estimation of LDL cholesterol by this method is not accurate. A more complex ultracentrifugation method in a specialized laboratory is required for accuracy. In addition, individuals with significantly elevated triglycerides need further evaluation.

The practical difficulties of obtaining fasting blood samples have resulted in a search for methods that directly measure LDL cholesterol in the nonfasting state. In recent years, several methods have been developed and standardized. Such methods will grow in use but still require careful quality control and monitoring. These methods do not require separation of LDL cholesterol and can be performed rapidly on automated machines. For initial testing, fasting triglycerides provide additional important information.

Most measurements are performed on venous samples from a phlebotomy. However, finger-stick methods are also widely available for total cholesterol, triglyceride, and HDL-cholesterol measurements. Careful attention must be paid to sample collection to minimize tissue fluid dilution. Sample handling is critical in obtaining accurate values from finger-stick samples. They

can produce accurate results when standardized by the same methods described for other laboratories.

The choice of laboratories is important to ensure accuracy and reliability in lipid measurements. Clinicians should seek a laboratory that participates in a recognized standardization program, preferably one standardized by the National Network Laboratories of the Centers for Disease Control and Prevention. More detailed information is provided in "Recommendations for Improving Cholesterol Measurement" from the Laboratory Standardization Panel of the NCEP (National Cholesterol Education Program. Recommendations . . . Measurement 1993) and in "Recommendations on Lipoprotein Measurement" from the NCEP Working Group on Lipoprotein Measurement (National Cholesterol Education Program 1995).

c. Classification of lipid and lipoprotein levels

In ATP II, initial classification for primary prevention was based on measurement of total cholesterol and HDL cholesterol. Because of increased availability of lipoprotein testing and to achieve more efficient evaluation, ATP III recommends measurement of LDL cholesterol for initial classification. This measurement requires a fasting lipoprotein analysis that includes total cholesterol, HDL cholesterol, triglycerides, and an estimate of LDL cholesterol. ATP III classifications of these four lipid and lipoprotein parameters were shown in Tables II.2–4, II.3–2, II.3–1, and II.2–4, respectively. Persons with very high LDL-cholesterol concentrations can have one of several familial forms of hypercholesterolemia (see Section VII).

d. Secondary dyslipidemias (see Section VII)

Any person who presents with elevated LDL cholesterol or other form of hyperlipidemia must undergo evaluation to rule out secondary dyslipidemia. The major causes of secondary dyslipidemia are shown in Table III.2–1. They include diabetes, hypothyroidism, chronic renal failure, nephrotic syndrome, chronic liver disease, and certain drugs that raise LDL cholesterol or triglyceride levels or lower HDL-cholesterol levels—particularly progestins, anabolic steroids, corticosteroids, and certain antihypertensive agents—and protease inhibitors (for persons with AIDS). The family, drug, and diet history may reveal clues to secondary causes of dyslipidemia. Patient history and physical examination can provide clues to diabetes, hypothyroidism, nephrotic syndrome, or liver disease. If a secondary dyslipidemia is suspected, urinalysis (for proteinuria), serum thyroid stimulating hormone (TSH) (for LDL cholesterol $\geq$160 mg/dL to rule out a masked form of hypothyroidism), and alkaline phosphatase (to detect obstructive biliary disease) should be measured. Glycosylated hemoglobin is a standard method for assessing the status of glucose control.

Table III.2–1. Major Causes of Secondary Dyslipidemia

• Diabetes
• Hypothyroidism
• Nephrotic syndrome
• Obstructive liver disease
• Chronic renal failure
• Drugs (that may raise LDL cholesterol or cause other dyslipidemias) – Progestins – Anabolic steroids – Corticosteroids – Protease inhibitors for treatment of HIV infections

3. Atherogenic dyslipidemia and the metabolic syndrome

a. Atherogenic dyslipidemia and classification of serum triglycerides

Atherogenic dyslipidemia is defined by elevation of serum triglycerides, presence of small LDL particles, and low HDL-cholesterol levels. For clinical purposes, elevated triglyceride ($\geq$150 mg/dL) plus low HDL cholesterol (<40 mg/dL) defines atherogenic dyslipidemia. As previously discussed (Section II.6), these levels frequently denote the presence of the metabolic syndrome. Serum triglycerides are measured in the fasting state as part of lipoprotein analysis. The ATP III classification of fasting serum triglycerides was given in Table II.3–1. The various categories of elevated triglycerides are described in more detail in Section VII. Triglyceride levels $\geq$200 mg/dL indicate the need to identify non-HDL cholesterol as a secondary target of lipid-lowering therapy (see Section VII).

b. Diagnosis of the metabolic syndrome

As stated in Section II.6, the metabolic syndrome is identified in ATP III by the presence of three or more marginal or categorical risk factors (see Table II.6–1). Other components of the metabolic syndrome (insulin resistance and prothrombotic state) cannot be identified by routine clinical evaluation. However, in the presence of abdominal obesity, they can be assumed to be present to some degree.

4. Role of emerging risk factors in risk assessment

The relationship of emerging risk factors to CHD risk is considered in detail in Section II.5. Some of these factors are potential adjuncts to risk assessment, but they should not take priority over the major risk factors. Risk evaluation should first be carried out as described for the major risk factors. Measurement of emerging risk factors is optional. Emerging risk factors that can be

measured include elevations of Lp(a), remnant lipoproteins, small LDL, fibrinogen, homocysteine, high-sensitivity C-reactive protein, impaired fasting plasma glucose (110–125 mg/dL), and measures of subclinical atherosclerosis (myocardial ischemia by exercise testing, carotid inimal-medial thickness, and/or coronary calcium). Among these factors, measures of subclinical atherosclerosis appear to have the most potential usefulness for risk assessment in middle-aged or older persons in whom standard risk factors decline in predictive power for individuals. If measurements are made and if abnormalities are detected, physician judgment is needed whether to modify the risk assessment. Examples of where emerging risk factors might be integrated into ATP III risk assessment are the following: (a) to elevate persons with multiple risk factors and 10-year risk $\leq$20 percent to the category of CHD risk equivalent, and (b) to guide a decision about use of LDL-lowering drugs—after lifestyle changes—in persons with 0–1 risk factor who have an LDL cholesterol in the range of 160–189 mg/dL (see Section IV.2.c).

ATP III does not recommend routine measurement of any of the emerging risk factors for the purpose of risk assessment. They should be used for this purpose only in selected persons and then only on the basis of considered clinical judgment. Several of these tests are not readily available, not well standardized, and are relatively expensive. Therefore, if these tests are used to adjust risk estimates, the physician should be fully cognizant of their limitations; above all, they should not be given undue weight relative to the major risk factors.